Remarks

Prior to entry of this amendment, claims 33 and 37-40 are pending in the application. No claim amendments or other amendments are made. Thus, after entry of this amendment, **claims 33 and 37-40 are pending.** Applicants traverse all of the rejections of these claims.

35 USC 103

The claims are rejected in the Office action under response for obviousness (35 USC §103). MPEP 2141 sets out the basic considerations applying to obviousness rejections. These are:

(a) the claimed invention must be considered as a whole;
(b) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
(c) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention;
(d) reasonable expectation of success is the standard with which obviousness is determined.

Furthermore, MPEP 2142 confirms that a *prima facie* case of obviousness requires three basic considerations:

(i) suggestion or motivation, in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.
(ii) a reasonable expectation of success;
(iii) the prior art references must teach or suggest all the claim limitations.

The Rejections

1. Randazzo #1 and Roizman

Virology 211, 94-10, 1995 (Randazzo #1)

In this paper, the authors were concerned with a mouse **brain** tumor model and the potential promise of 1716 as a therapeutic agent for the treatment of **brain** tumors (see abstract).

In the introduction, the authors admit that "The mechanisms by which viruses improve the outcome in experimental tumor systems are complex and poorly understood". The authors continue to explain a rationale of treatment "in the context of **brain** tumor therapy" which involves selection of a virus that "replicates exclusively or preferentially in dividing cells". This rationale is considered as appropriate for **brain** tumors because of the **non-dividing background cell population** in the CNS.

The introduction continues to describe how the inventors sought to investigate treatment of **brain** tumor, and in particular to investigate a model of metastatic tumor occurring in the brain (*i.e.*, tumors occurring in, but not originating in, the brain). A metastatic melanoma model was selected because of its perceived clinical relevance (see page 95 col. 1 3rd paragraph and page 98 col. 2 2nd paragraph).

The last sentence of the introduction summarizes the finding that 1716 "is a safe and effective therapeutic agent for **intracranial** melanoma", *i.e.*, for a **brain** tumor.

Prior to creation of the intracranial tumor model, three melanoma cell lines were tested **in vitro**. Administration of 1716 resulted in lysis in two of the three cell lines tested, the authors were "surprised to find that B-16 was completely resistant to lysis by all of the HSV-1 isolates tested" (page 98 col. 2 last paragraph). H-P and B-16 cells formed intracranial tumors in all cases, but S-91 achieved only 10% success in this regard (page 96 col. 2). The authors proceeded with the H-P model because the cells were susceptible to lysis and formed brain tumors effectively.

It is also noted that the authors report lysis ***in vitro*** by 1716 of 26 out of 26 human melanoma cell lines, although details of these experiments are not provided (page 99 col. 1).

It is necessary to consider the teaching provided by this paper when considered as a whole. From the paper, one can say that 1716 is effective to lyse many, but not all, melanoma cell types ***in vitro***. That is, 1716 can lyse these particular **dividing** cell types ***in vitro***.

In vivo, one melanoma cell type (H-P) was used to create an intracranial tumor model. This model is not of a primary tumor but of a **secondary or metastatic tumor**, *i.e.*, melanoma metastatic to the brain. The authors indicate that lysis of these particular intracranial tumors may be due to the tumor presenting a dividing cell population within an essentially non-dividing cell population formed by the support cells and terminally differentiated neurons of the brain and central nervous system (CNS).

Thus, the paper indicates that the therapeutic efficacy of 1716 involves selective lysis of dividing cells, in this case tumor cells (this is recognized at the paragraph bridging col. 1 and col. 2 on page 94).

The *in vitro* data provides no information as to selectivity; it simply indicates that many melanoma cell lines can be lysed *in vitro*. The *in vivo* data all relate to intracranial tumor, *i.e.*, tumors occurring in the brain, where it is recognized that the tumor is an isolated dividing cell population amongst a tissue consisting of non-dividing cells. That is, the lytic selectivity of 1716 *in vivo* is taught, in this paper, to be a function of the nature of the cell type which is infected – *i.e.*, if it is dividing then 1716 may lyse that cell, if it is not dividing, 1716 will not lyse the cell. The paper does not teach 1716 to be selective in itself for lysis of tumor cells whilst not lysing non-tumor dividing cells.

This may be considered as an inventive concept, that selective lysis of tumor cells by 1716 is not the result of unscrupulous lysis of dividing cells situated in a background of non-dividing cells, but it is 1716 itself that is capable of selective lysis of tumor cells.

With reference to the present application, the teaching of the paper is that 1716 may provide a therapeutically effective lysis of tumor cells when those cells occur in a non-dividing background cell population.

US 6,340,673 (Roizman)

Roizman does not teach the treatment of a non-neuronal tumor, nor does it relate to the specific virus HSV-1 1716.

Applicant is aware that examiner will consider Roizman enabled across the scope of the claims. In determining that scope, the claims must be construed in conjunction with the description, which, in as far as the Roizman application relates to treatment of tumors only discusses **primary neuronal** tumors, usually neuroblastoma cells ***in vitro***.[1] The term neuronal tumor is indicative of the origin of the tumor, *i.e.*, neuronal cells, and the cells tested are primary tumor cells.

Roizman did attempt to investigate the function of the γ34.5 gene. The results are briefly described at col. 18 lines 9-15. Whilst not entirely clear, a distinction is drawn between infection of cells of neuronal origin and cells of non-neuronal origin, in that replication occurs in the latter and is comparable to infection with wild type virus. The Examiner will note that replication does not necessarily result in lysis of cells (the replicative cycle may be latent) but is required in order for that to occur.

Combining Randazzo #1 and Roizman

The Examiner is correct in that Roizman does not teach a method for treating a non-neuronal cancer in a mammal using HSV-1 1716. The question is, does Randazzo #1 in combination with Roizman teach this with a reasonable expectation of success? Applicant contends that this combination does not.

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[1] In this respect careful consideration of the examples in Roizman is a useful exercise:

- Example 1 – this relates to impact on programmed cell death and is performed *in vitro* in Vero cells and SK-N-SH neuroblastoma cells;
- Example 2 is speculative and does not appear to have been performed, and in any event refers to gene therapy;
- Example 3 relates to methods of introduction of the γ34.5 gene to the CNS by the use of cell lines passaged *in vitro*.
- Example 4 relates to treatment of cells by the protein expressed by the γ34.5 gene;
- Example 5 is concerned with screening for substances that mimic the function of γ34.5 to prevent neurodegeneration. The experiments are all performed *in vitro* in neuroblastoma or Vero cells;
- Example 6 mentions induction of cell death in tumor cells, but is concerned with screening for substances which trigger cell death in tumor cells. Again, the experiments are performed *in vitro* using specific cell lines.

There are no experimental teachings in Roizman regarding the treatment of tumors *in vivo*.

Randazzo #1 is teaching that the success of treating neuronal tumor types with 1716 is based on the presence of dividing cells in the form of tumor cells wherein 1716 indiscriminately lyses and kills those dividing cells. The implication is that, were there to be other dividing cells present in the CNS environment, they too would be lysed and killed. Roizman does not teach to the contrary, and indicates that replication in non-neuronal cells may occur in a manner similar to that observed for wild type virus.

One distinction which can be drawn between neuronal tissue types and non-neuronal tissue types, *e.g.*, the skin, is in that the former contains terminally differentiated and **non-dividing** cells whilst the latter does not. Skin cells (melanocytes) are a good example of this – it is well known that skin cells include dividing basal layer cells responsible for continual regeneration of the skin.

Applying the teaching of Randazzo #1 to the skin, one might expect HSV-1 1716 to result in lysis of tumor cells (probably melanoma cells), but one would also expect lysis of healthy non-tumor dividing cells to occur. Clearly this would not provide a safe and effective treatment in that the healthy dividing cells of the skin would also be killed which would be detrimental to the health of the patient. The result is that no method of treatment of non-neuronal cancer, which must necessarily be beneficial, effective and most preferably safe in order for it to be considered a 'treatment', is provided when the teaching of Randazzo #1 and Roizman is combined. Applicant therefore requests that the rejection of the claims based on this combination be withdrawn.

2. Randazzo #1, Roizman and Martuza

US 6,139,834 (Martuza)

The Examiner has made further rejection based on Martuza. The Examiner's comments only relate to claim 40, and Applicant understands that it is the features of this claim, in appropriate combination with those of claim 33, which is the subject of the rejection.

It follows that where claim 33 is non-obvious, claim 40 is also non-obvious due to the claim dependency. In view of the comments made above, Applicant contends that this is the

case and the rejection should be withdrawn. Nevertheless, to provide a complete response, consideration has been given to Martuza.

Martuza relates to a herpes simplex virus vector altered in two ways – (i) in the γ34.5 gene; and (ii) in the ribonucleotide reductase gene. For example, see claim 1 and col. 1 line 16:

> "...the present invention relates to a mutated, replication-competent Herpes Simplex virus-1 (HSV-1) which contains mutations in two genes...".

These two features are present throughout the Martuza disclosure and are essential features of Martuza. Any teaching afforded to the skilled person by Martuza must recognize that the result in Martuza is attributable to this combination of mutations. The contribution of each mutation to the properties of the disclosed mutant virus is not separable. The disclosure is only enabled in as far as the teaching of the document extends and that teaching is clearly limited to a virus having two mutations, the contribution of each mutation to the result not being individually assessed or disclosed.

Martuza only describes one experiment in which tumor cells are treated. This is Example 3 and considers an *in vivo* extracranial model comprising a glioma (primary brain tumor) xenograft. In the words of the cited patent, this was "To test the effect of the herpes simplex virus mutants on human glioma in vivo". Thus, it is clear that the teaching of this example relates to glioma, *i.e.*, neuronal tumor.

Examples 4-8 are all speculative and were not performed.

Combining Martuza with Randazzo #1 and Roizman

In the context of claim 40, before a meaningful combination can be contemplated it must first be possible to combine Randazzo #1and Roizman to render claim 33 obvious. Applicant submits that this is not possible and the rejection based on the further combination with Martuza is inappropriate and should be withdrawn.

Even if one were to make the combination, two issues are relevant. First the list of tumor types in Martuza at col. 3 lines 49-67 is speculative. The examples in Martuza are concerned with neuronal tumors and the tumor types mentioned in this passage are not of that kind. Second, any teaching of tumor types which can be treated in Martuza must take into account the overall teaching of Martuza, which is that a double mutation is required. Consequently any teaching taken from Martuza must include that of a ribonucleotide reductase mutation. As discussed above, this teaching is not separable from the remainder of Martuza, indeed it is essential to Martuza.

To take the tumor types mentioned in Martuza, and cited by the Examiner, in isolation from the remainder of the teaching and combine them with Randazzo #1 and Roizman would be to make an inappropriate and abstract combination ignoring the context and teaching of the cited art.

Thus, the specific non-neuronal tumor types mentioned in Martuza are not available for combination with the teachings of Randazzo #1 and/or Roizman, because any teaching taken from Martuza must carry with it the ribonucleotide reductase mutation and should be confined to neuronal tumor types. The result is that the subject-matter claimed in claim 33 or claim 40 cannot be reached by such combination. Applicant therefore requests that this rejection be withdrawn.

Duty of Disclosure

Examiner is made aware of, and is directed to consider, the co-pending and co-owned US patent application serial number 08/776,350.

Conclusion

The Examiner is invited to telephone the undersigned if any questions remain concerning the amendments made herein. Otherwise, the present application is ready for substantive examination, and such action is requested.

Respectfully submitted,

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